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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/579,825	05/17/2006	Dirk Finsinger	MERCK-3165	5742

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EXAMINER	
BIANCHI, KRISTIN A	
ART UNIT	PAPER NUMBER
1626	

MAIL DATE	DELIVERY MODE
12/22/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/579,825	FINSINGER ET AL.	
	Examiner	Art Unit	
	KRISTIN BIANCHI	1626	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *04 November 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-34* is/are pending in the application.

4a) Of the above claim(s) *15-27* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-14 and 28-34* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *05/17/2006*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-34 are pending in the instant application. Claims 15-27 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to non-elected subject matter. The withdrawn subject matter is patentably distinct from the elected subject matter as it differs in structure and element and would require separate search considerations. In addition, a reference which anticipates one group would not render obvious the other. Claims 1-14 and 28-34 are rejected.

Information Disclosure Statement

The information disclosure statement filed on May 17, 2006 was considered and a signed copy of form 1449 is enclosed herewith.

Election/Restrictions

Applicant's election with traverse of Group I and the compound N-methyl-4-{4-[5-(4-chloro-3-trifluoromethylmethylphenylcarbamoyl)-1H-pyrrol-3-yl]phenoxy}pyridine-2-carboxamide in the response filed on November 4, 2008 has been acknowledged.

The traversal is on the ground(s): "the compounds of formula I as recited in claim 1 and the compounds of formula I-1 recited in claim 26 share a substantial common core structure... there is no significant burden in examining all of the compounds together." This argument is not found to be persuasive because as presented in the restriction requirement dated October 24, 2008, “Group I and Group II comprise structurally different compounds which do not have a common core structure within the chemical structure of each compound (i.e. in Group I, NH is bonded to C=Y whereas in Group II, OR is bonded to C=O).” Since claims 15-25 were converted into method

claims, they will be restricted into their own group (i.e. Group III). This is considered proper since it was demonstrated in the restriction requirement dated October 24, 2008 that the compounds are not so linked by the same or a corresponding special technical feature as to form a single general inventive concept (i.e. as described above). Newly added claim 28-34 will be added to Group I.

The requirement is still deemed proper and is therefore maintained.

Upon further consideration, the requirement to elect a specific compound is withdrawn and the claims of Group I, claims 1-14 and newly added claims 28-34, have been search and examined in their entirety.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-14 and 28-34 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the compounds of formula I, pharmaceutically usable salts or stereoisomers thereof, does not reasonably provide enablement for pharmaceutically usable derivatives or solvates thereof. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Enablement is considered in view of the Wands factors (MPEP 2164.01 (A)). These include: nature of the invention, breadth of the claims, guidance of the

specification, the existence of working examples, state of the art, predictability of the art and the amount of experimentation necessary. All of the Wands factors have been considered with regard to the instant claims, with the most relevant factors discussed below.

The state of the prior art/level of ordinary skill/level of predictability

In regards to "pharmaceutically usable solvates," active pharmaceutical ingredients are frequently delivered to the patient in the solid-state as part of an approved dosage form (e.g., tablets, capsules, etc.). Solids provide a convenient, compact, and generally stable format to store an active pharmaceutical ingredient or a drug product. Understanding and controlling the solid-state chemistry of active pharmaceutical ingredients, both as pure drug substances and in formulated products, is therefore an important aspect of the drug development process. Active pharmaceutical ingredients can exist in a variety of distinct solid forms, including polymorphs, solvates, hydrates, salts, co-crystals, and amorphous solids. Each form displays unique physicochemical properties that can profoundly influence the bioavailability, manufacturability purification, stability, and other performance characteristics of the drug. Hence, it is critical to understand the relationship between the particular solid form of a compound and its functional properties.

For ionizable compounds, preparation of salt forms using pharmaceutically acceptable acids and bases is a common strategy to improve bioavailability. However, the preparation of other solid forms, such as polymorphs, solvates and hydrates, are not so common to be predictable. In order to obtain patent protection on these forms, some

of which may have significantly different properties and relevance as development candidates, it is essential to prepare them, identify conditions for making them, and evaluate their properties as valuable new pharmaceutical materials.

Therefore, for the reasons above, the state of the prior art is one of unpredictability.

As stated above, crystalline solids can exist in the form of polymorph, solvates or hydrates. "Phase transitions such as polymorph interconversion, desolvation of solvate, formation of hydrate, and conversion of crystalline to amorphous form may occur during various pharmaceutical processes, which may alter the dissolution rate and transport characteristics of the drug. Hence, it is desirable to choose the most suitable and stable form of the drug in the initial stages of drug development" (Vippagunta et al., abstract). In further discussing the predictability of the formation of solvates, Vippagunta et al. discloses that "predicting the formation of solvates or hydrates of a compound and the number of molecules of water or solvent incorporated into the crystal lattice of a compound is complex and difficult. Each solid compound responds uniquely to the possible formation of solvates or hydrates and hence generalizations cannot be made for a series of related compounds" (page 18, section 3.4).

In regards to “pharmaceutically usable derivatives,” this is defined in the specification (page 16, lines 9-11) as “the salts of the compounds according to the invention and also so-called prodrug compounds.”

“Pro-drugs" are commonly known in the art as drugs which are administered in an inactive (or less active) form, and then metabolized in vivo into an active metabolite.

Wolff et al. (Burger's Medicinal Chemistry, 5th Ed., Vol. 1, pages 975-977, 1994) summarizes the state of the prodrug art, the lengthy research involved in successfully identifying a prodrug and the difficulties of extrapolating between species.

The level of skill of the pharmacological art involves screening *in vitro* and *in vivo* to determine which compounds exhibit the desired pharmacological activities as prodrugs. There is no absolute predictability even in view of the seemingly high level of skill in the art. The existence of these obstacles establishes that the contemporary knowledge in the art would prevent one of ordinary skill in the art from accepting any prodrug on its face, without evidence to support that particular prodrug. It is noted that the pharmaceutical art is unpredictable and requires the embodiments to be individually assessed for physiological activity. Each embodiment of a prodrug must be supported by this invention in order to be enabled for the full range of prodrugs of said compounds.

With the limited direction and exemplification the specification offers, it is highly unpredictable that said compounds will actually form effective prodrugs thereof. The evidence supports the conclusion that the method of making claimed prodrugs is a subject for further study and experimentation.

The amount of direction or guidance present/existence of working examples

A disclosure should contain representative examples which provide reasonable assurance to one skilled in the art that the compounds which fall within the scope of a claim will posses the alleged activity. The specification does not adequately enable a method of making prodrugs or solvates of the compounds that the claims encompass.

There is no data present or any working examples in the specification for the preparation of prodrugs or solvates of said compounds.

As discussed above, it would be necessary for Applicant to provide evidentiary support for each embodiment due to the unpredictability in the art with regards to the success of prodrugs with some drugs over others.

The quantity of experimentation needed

While the level of skill in the pharmaceutical art is high, it would require undue experimentation for one of ordinary skill in the pertinent art to prepare any solvate or prodrug of said compounds.

The specification provides limited support, as noted above, for the prodrugs or solvates encompassed by the claims. The quantity of experimentation needed to make the prodrugs or solvates encompassed by the claims would be an undue burden on one skilled in the chemical art, since the skilled artisan is given inadequate guidance for the reasons stated above. Even with the undue burden of experimentation, there is no guarantee that one would obtain the desired prodrugs in view of the Wolff et al. reference. Also, the science of crystallization has evolved such that, without guidance or working examples in the specification, the claim lacks enablement.

This discussion established *prima facie* non-enablement. Deletion of the words "solvate," and "derivative" from claim 1 would overcome this rejection.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

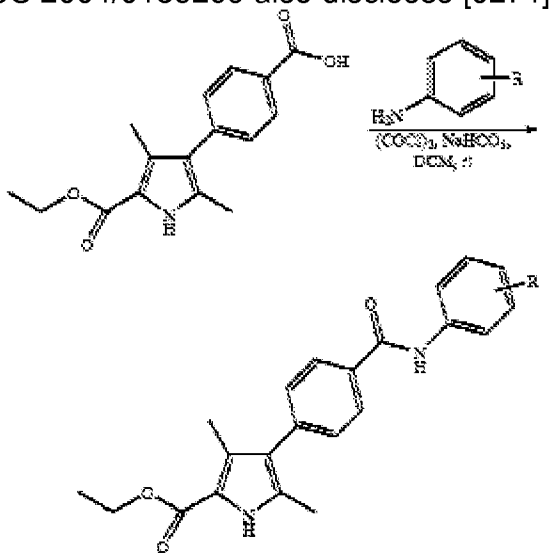
1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 1-14 and 28-34 are rejected under 35 U.S.C. 103(a) as being unpatentable over US 2004/0138269.

Determination of the scope and contents of the prior art.

US 2004/0138269 discloses substituted pyrroles which modulate the activity of protein kinases (abstract), such as the preferred embodiments of Formula II [0034] (and Formulas I and III, [0020] and [0048], respectively) which includes the scope of the compounds of the instant claims when R1, R3 and R4 of Formula II (and Formulas I and III) are hydrogen, R5 is -NR6R7 wherein one of R6 or R7 is hydrogen with the remaining being aryl, arylakyl, alkylaryl, or heteroaryl, A is phenyl, L is -NR8- or -O-, and B is aryl or heteroaryl.

US 2004/0138269 also discloses [0271] the following reaction:



Ascertaining the differences between the prior art and the instant claims.
US 2004/0138269 does not disclose specific compounds which fall within the scope of the instant claims or compounds in which L of Formula II (or Formula I or III) is -NR8- or -O-.

The reaction disclosed in US 2004/0138269 is the same reaction as disclosed in claim 13 of the instant application except that the -C(O)-OH group is attached to a phenyl in US 2004/0138269 whereas it is attached to the pyrrole in the instant claim (i.e. both are aromatic rings, however).

Resolving the level of ordinary skill in the pertinent art -- Prima Facie Case of Obviousness.
It would have been obvious to one of ordinary skill in the art at the time of the invention to prepare the compounds of the instant case given US 2004/0138269 since the *preferred* formulas of US 2004/0138269 (i.e. I, II and III) include the scope of the compounds of the instant claims and because the compounds of US 2004/0138269 are used for the same purpose as the compounds of the instant claims. One of ordinary skill would be motivated from US 2004/0138269 to make the compounds of the instant claims with reasonable expectation of success for obtaining compounds with the same activity. The motivation would be to make additional compounds which can be used for the quoted purpose.

One of ordinary skill would also be motivated to carry out the reaction disclosed in claim 13 of the instant case given the reaction disclosed in US 2004/0138269 with reasonable expectation of success for obtaining compounds with the same activity.

Thus, the instant claims are *prima facie* obvious over the teaching of the prior art.

Claims 1-3, 6, 7, 11, 14, 28, and 29 are rejected under 35 U.S.C. 103(a) as being unpatentable over US 2008/0234270 (since the provisional applications are fully supportive of the subject matter which is used in this rejection, the filing dates of these applications can be used as the 102(e) date).

Applicant cannot rely upon the foreign priority papers to overcome this rejection because a translation of said papers has not been made of record in accordance with 37 CFR 1.55. See MPEP § 201.15.

Determination of the scope and contents of the prior art.
US 2008/0234270 discloses pyrrole derivatives which are used for modulating the activity of receptors, such as compound 673 on page 292.

Ascertaining the differences between the prior art and the instant claims.
The compound disclosed in US 2008/0234270 only differs from a compound of the instant claims wherein X is -O-, Ar is phenyl and Z is phenyl which is substituted with S(O)mA wherein m is 2 and A is methyl by having two methyl groups on the pyrrole ring.

Resolving the level of ordinary skill in the pertinent art -- Prima Facie Case of Obviousness.
To those skilled in the chemical art, one homologue is not an advance over an adjacent member of a homologous series. The reason for this is that one of ordinary skill, knowing the properties of one member of a series, would know what properties to expect in adjacent members. In re Henze, 85 USPQ 261 (1950). In re Wood, 199 U.S.P.Q. 137 (C.C.P.A. 1978) and In re Lohr, 137 U.S.P.Q. 548, 549 (C.C.P.A. 1963).

It would have been obvious to one of ordinary skill in the art at the time of the invention to make the modifications necessary (i.e. change the two methyl groups on the pyrrole ring to hydrogen) to arrive at a compound of the instant claims with reasonable expectation of success for obtaining a compound with the same activity given US 2008/0234270. The motivation would be to make additional compounds which can be used for the quoted purpose.

Thus, the instant claims are *prima facie* obvious over the teaching of the prior art.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to KRISTIN BIANCHI whose telephone number is (571)270-5232. The examiner can normally be reached on Mon-Fri 7am-3:30pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph McKane can be reached on 571-272-0699. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Kamal A Saeed/
Primary Examiner, Art Unit 1626

Kristin Bianchi
Examiner
Art Unit 1626

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